CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 50-778

Medical Review(s)

Medical Officer NDA Review: Epirubicin hydrochloride
Medical Officer: Susan Flamm Honig, M.D.
Team Leader: Grant Williams, M.D.

9/2/99

1.0 General Information

1.1 NDA Information

1.1.1 NDA number NDA 21-010 (changed to 50-778)
1.1.2 Submission date: December 15, 1998
1.1.3 Completion Date: May 18, 1999

1.2 Drug Name

1.2.1 Generic Name: Epirubicin hydrochloride (4′-Epi-adriamycin; 4′-Epidoxorubicin hydrochloride)
1.2.2 Trade Name: To be determined
1.2.3 Chemical Name: (8S, 10S)-10-[(3-amino-2,3,6-trideoxy-α-L-arabino-hexopyranosyl)oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphtacenedione hydrochloride

1.3 Sponsor: Pharmacia and Upjohn Company

1.4 Pharmacologic Category: Anthracycline antitumor antibiotic (4′-epimer of doxorubicin); DNA intercalation; topoisomerase II inhibition

1.5 Proposed Indication: As a component of adjuvant therapy in patients with node positive breast cancer

For therapy of patients with locally advanced or metastatic breast cancer

1.6 Dosage Form and Route of Administration: Solution for IV injection

1.7 NDA Drug Classification: Priority

1.8 Related INDs and NDAs: IND [redacted] NDA 50-595

1.9 Foreign Marketing: Approved in 80 countries worldwide under variations of the trademark Pharmorubicin (Farmorubicin, Farmorubicina, Farmorubicine). First approved in France in 1982. Indications include breast, ovarian, lung, stomach, liver, pancreatic, and bladder cancer; sarcoma; lymphoma

Breast cancer: Approved at doses of 100-120 mg/m^2 every 3-4 weeks.

3.0 Material Reviewed/Clinical Data Sources/Administrative Review

3.1 Source

The NDA was submitted December 15, 1998 and consisted of 69 volumes. The pharmacokinetic section (Item 5) was presubmitted on November 5, 1998 and consisted of volumes 1.1-1.27. Volumes 1.28 through 1.34 contained the human pharmacokinetic and bioavailability data and were also pre-submitted. Case Report Forms (CRF) and Case Report Tabulations (CRT) were submitted in electronic format only, as agreed upon in the pre-NDA meeting.

Two indications are sought by the sponsor, one for early breast cancer and one for metastatic breast cancer.

For early breast cancer:

- Study MA-5 (CEF 120 vs. CMF) is considered the pivotal trial.
- Study GFEA05 (CEF 100 vs. CEF 50) provides confirmation of the activity of the regimen.
- (data not submitted for review).

For advanced breast cancer:

- Study HEPI013 (CEF 100 vs. CMF) is the pivotal trial.
- Study HEPI010 (CEF 100 vs. CEF 50) is the supportive study.
- Study BE-85008 (CEF 100 vs. CEF 50) and Study 068093 (epi 135 vs. epi 75) are additional supportive trials for this indication (data not submitted for review).

Farmitalia was former name of Pharmacia + up John

3.2 Administrative review

3.2.1 Previous administrative history

An IND for epirubicin was opened by Farmitalia in ***April 1979***. Epirubicin was investigated in a variety of oncologic settings. A pre-NDA meeting was held 9/29/83 with the DODP; more data were required in order to substantiate a submission for treatment of breast cancer. The importance of determining the contribution of epirubicin to combination drug regimens and the effect of epirubicin on survival was also discussed.

A NDA was submitted 7/13/84 for the treatment of advanced breast cancer. Thirty-six studies, including 5 designated as pivotal, were included. The five pivotal trials were:

- Trial ID-7: A prospective randomized comparison of doxorubicin and a less cardiotoxic analog in patients with advanced breast cancer (54 patients)
- ID-5: A prospective clinical trial comparing 4-epidoxorubicin versus doxorubicin in patients with advanced breast cancer resistant to conventional therapies (47 patients)
- ID-8: Phase III clinical trial comparing 5-FU, doxorubicin, cyclophosphamide versus 5-FU, 4'-epidoxorubicin, cyclophosphamide in advanced breast cancer (196 patients)
- ID-6: Phase II trial of carminomycin and epirubicin in advanced breast cancer (68 patients)

- ID-4: Comparative study of continuous 48-hour infusion of Adriamycin vs. epirubicin by bolus injection or 48-hour infusion in patients with metastatic breast cancer who have been previously exposed but not known to be resistant to Adriamycin, or patients not previously exposed to Adriamycin (68 patients)

All of these trials were considered by the medical reviewer to have the same limitations: few patients, incomplete descriptions of the protocol and of the statistical methodology, inappropriate exclusion of randomized patients, lack of survival data, and lack of primary data submitted for independent confirmation of reported results. The statistical reviewer noted that all of the trials enrolled insufficient patients to demonstrate that epirubicin was as effective as doxorubicin, the concurrent control. The statistical report provided for each study by the sponsor was not always consistent with the clinical report for that trial. Data on cardiotoxicity were not well-controlled, and were analyzed based on number of endomyocardial biopsies rather than on a per-patient basis. The Biopharmaceutical reviewer noted that incomplete documentation to fulfill Code of Federal Regulations (CFR) requirements for pharmacokinetic and biopharmaceutic issues was provided. Finally, several deficiencies were noted by the Chemistry reviewer. ***A non-approval letter was issued July 10, 1985.*** At that time, the sponsor decided not to submit responses to the deficiency list. The IND was closed, and no further investigations with epirubicin were conducted in the United States.

3.2.2 Current administrative history

Pre-NDA meeting, April 9, 1998

On April 9, 1998, a pre-NDA meeting was held with the sponsor (now called Pharmacia and Upjohn) to discuss the possibility of submitting a NDA for both early stage and advanced breast cancer. The DODP agreed that the submitted summaries appeared to support NDA submission. For first-line therapy of metastatic breast cancer, meta-analyses have demonstrated a modest survival advantage for doxorubicin-based regimens; approval in this setting is contingent on the demonstration of non-inferiority of the proposed drug to doxorubicin. The sponsor was advised that trials of doxorubicin-based therapy should be described and compared to epirubicin-based therapy in order to demonstrate the non-inferiority of epirubicin to doxorubicin in this first-line setting. The sponsor was advised to request a meeting with the chemists.

Reactivation of IND —

The IND was reactivated to allow pre-submission of part of the planned NDA and to allow for additional communication between the sponsor and the Agency.

Pre-NDA meeting, July 23, 1998

A second pre-NDA meeting was held to resolve additional issues and questions identified by the sponsor. Because of the extensive published literature on epirubicin, the guidelines for submission of appropriate pharmacokinetic, biopharmaceutic, and clinical articles were discussed and agreed upon. The need for primary data, the requirement for translated CRF documents, and a detailed doxorubicin/epirubicin comparison to

demonstrate non-inferiority were documented. Reference papers to facilitate the comparative review were provided to the sponsor.

Chemistry meeting, July 23, 1998

The requirements for chemistry and manufacturing standards and submissions were discussed.

General Correspondence, September 17, 1998

Both the medical and statistical reviewers provided guidance on the proposed non-inferiority analysis. The company submitted a proposal for the translation of CRFs from study GFEA05 that was accepted by FDA.

Request for trademark review, October 21, 1998

This request remains under review.

3.2.3 Amendments and correspondence submitted to the NDA/IND

During the course of the NDA review, the reviewer sent requests for information to the sponsor on 1/28, 2/2, 2/5, 2/11, 2/17, 2/18, 2/23, 2/26, 3/4, 3/4, 3/25, 4/15, 5/6, and 5/7.

The following list summarizes additional responses/submissions by the sponsor.

Response to FDA Request for Information (RFRI) February 12, 1999 (sponsor's Amendment 001)

The sponsor addressed two questions sent by the FDA on 1/29/99.

Amendment 2, February 15, 1999

The sponsor submitted the CRFs for study GFEA05 electronically.

IND — N (238) February 22, 1999

Periodic Safety Report for epirubicin from July 1, 1993 to June 30, 1998

RFRI February 24, 1999 (sponsor Amendment 003)

The sponsor provided part of the information requested 2/2/99.

RFRI February 25, 1999 (sponsor's Amendment 004)

The sponsor provided answers to 4 of 10 questions sent 2/5/99.

Amendment 005 March 2, 1999

The sponsor resubmitted the electronic clinical chemistry files for advanced breast cancer because of a data entry problem.

RFRI March 3, 1999

The sponsor provided line listings of adverse events for the DSI audit.

RFRI March 4, 1999 (sponsor's amendment 7)
The sponsor provided responses to the remainder of the questions sent 2/5/99.

RFRI March 5, 1999 (sponsor's amendment 7—sponsor numbering error)
The sponsor provided responses to 5 of the 7 questions sent 2/17/99.

RFRI March 5, 1999 (sponsor's amendment 8)
The sponsor provided responses to the remainder of the questions sent 2/26/99.

RFRI March 22, 1999 (sponsor's amendment 9)
The sponsor provided responses to all but one question sent 3/5/99.

RFRI March 25, 1999 (sponsor's amendment 10)
The sponsor provided responses to the remainder of the questions sent 2/17/99.

Four month safety update April 13, 1999 (sponsor's amendment 12)
This update included adverse events reported from October 21, 1998 through March 15, 1999.

RFRI April 28, 1999 (sponsor's amendment 13)
The sponsor provided answers to 4 of 10 questions sent 3/25/99 and to all questions sent later on 3/25/99.

RFRI May 4, 1999 (sponsor's amendment 15)
The sponsor provided answers to one question sent 3/5/99 (clarification sent 3/25/99) and to the remaining 6 questions sent 3/25/99.

RFRI May 7, 1999 (sponsor's amendment 16)
The sponsor provided answers to 9 of 10 questions sent 4/15/99.

RFRI May 11, 1999 (sponsor's amendment 18)
The sponsor provided answers to a facsimile sent 5/6 regarding the DSI audit report, and to the remaining question from 4/15/99.

Submission 5/13/99 (sponsor's amendment 19)
ODAC briefing package

RFRI May 14, 1999 (sponsor's amendment 20)
The sponsor replied to all questions sent May 7, 1999.

3.2.4 Other labeled drugs for these indications

There are no cytotoxic agents specifically labeled for adjuvant breast cancer treatment. Cyclophosphamide, methotrexate, and doxorubicin were approved between 1953 and 1974 and received a broad indication for "breast cancer" treatment. 5-Fluorouracil was approved in 1962 as palliative therapy for breast cancer.

No cytotoxic agents have a specific indication for first-line therapy of metastatic breast cancer. Taxotere was approved for breast cancer treatment after failure of prior chemotherapy. Capecitabine was approved to treat patients resistant to anthracyclines and taxanes.

Herceptin in combination with paclitaxel has been approved for first-line therapy of metastatic breast cancer in women whose tumors overexpress erbB-2.

If approved, epirubicin will be the first drug to obtain these specific indications for breast cancer treatment.

3.3 Key volumes

NDA report item	VOLUME
Detailed index to the application	2.1, Tabs 4-10
Label	2.2; repeated in volume 2.3
Summaries:	All in volume 2.3
Pharmacology	
Marketing history	
CMC	
Biopharmacology	
Clinical trials	
Chemistry	Volumes 2.4-2.9 (Chemistry reviewer only)
Clinical Pharmacology	Volumes 2.10-2.18
Early breast cancer trials:	
MA-5	Volumes 2.19-2.27
Study report	Volume 2.19
Protocol document	Volume 2.20
Quality of life analysis	Volume 2.27
GFEA05	Volumes 2.28-2.32
Advanced breast cancer trials:	
HEPI013	Volumes 2.33-2.43
HEPI010	Volumes 2.44-2.52
Supportive trials	Volumes 2.53-2.54
Epirubicin v. doxorubicin as first-line therapy of MBC	Volume 2.58
World-wide marketing/Safety	Volume 2.55
ISE, ISE	Volume 2.59
Summary of risks and benefits	Volume 2.60
Selected bibliography	Volumes 2.55-2.57; 2.61-2.65
Investigator CVs	Volumes 2.66-2.69

4.0 Chemistry/Manufacturing Controls

Please see the Chemistry review by Sung Kwang Kim, Ph.D.

Epirubicin was originally formulated as a freeze-dried powder that required reconstitution at the clinical site with limited stability. All of the submitted clinical trials used this formulation and were initiated in the late 1980s. It was not possible for the sponsor to trace the batch numbers from the manufacturing site, match them with the numbers assigned by the countries used as trial sites, and specifically correlate the quality and purity of the batches of drug used in the clinical trials with that of the drug formulation proposed for registration. The sponsor has instead presented a summary of batch results for the freeze-dried powder, organized by year, which have been compared to the to-be-marketed formulation. The Chemistry reviewer will determine whether the specifications are acceptable.

Epirubicin is currently available as a sterile, preservative-free ready-to-use solution for IV use. It has been marketed in glass ampules, but recently a formulation packaged in polypropylene vials was approved in many non-U.S. countries and will be used as the NDA formulation. The drug is stable for 24 months when refrigerated and protected from light.

During its synthesis from daunorubicin, there is the possibility of isomerization; the isomer produced by this process is doxorubicin. The amount of isomer contamination is small. The sponsor has submitted documentation of its synthetic process; the Chemistry reviewer will determine whether there is acceptable proof of drug substance. From a clinical viewpoint, isomerization is unlikely to affect the outcome of the trial, given the close chemical relationship and similar spectrum of activity and toxicity of doxorubicin and epirubicin.

5.0 Animal Pharmacology/Toxicology

Please see Pharmacology/Toxicology review by Doo Young Lee-Ham, Ph.D. and the Biopharmaceutics review by Safaa Ibrahim, Ph.D.

Most of the pre-clinical studies with epirubicin, including toxicology studies, were performed in the late 1970s and early 1980s, and therefore do not conform to current Good Laboratory Practices (GLP) regulations. These issues were discussed during the pre-NDA meeting. The breadth of experience with epirubicin and the large size of the published literature ensure that the pharmacokinetic properties of the drug have been adequately investigated.

5.1 Pharmacodynamics

Epirubicin demonstrates broad activity against cell lines and *in vivo* nude mouse xenograft model systems. Cytotoxicity is related to dose and to duration of exposure. Epirubicin demonstrates cross-resistance to doxorubicin in animals. Its efficacy compared to doxorubicin varies with the model system examined and the schedule of drug administration. Preclinically, epirubicin has been found to have a higher therapeutic index than doxorubicin and has been considered to be less toxic.

5.2 Toxicology

The acute toxicity of epirubicin affects bone marrow function, the GI tract, the testes, kidney (chronic progressive nephrosis), and liver (transaminase elevation). Epirubicin produced less severe toxicity than doxorubicin. In these animal studies, cardiac toxicity was not observed because of early death from myelosuppression.

Chronic administration of epirubicin significantly affects hematopoiesis, the organ systems affected by acute administration, and the heart. Epirubicin-induced cardiomyopathy occurred 2-4 weeks after single or repeated doses of epirubicin in animals and was irreversible. The observed cardiotoxicity was 54% less than that produced by doxorubicin in single-dose studies, and 34% less than that produced by doxorubicin in multiple-dose studies. Cardiac toxicity is more pronounced in animals than in man, because glucuronidation of epirubicin in humans produces less toxic metabolites; the glucuronidation pathway is absent in animals. Like doxorubicin, epirubicin produced neurotoxicity and mucositis in animals treated with high doses.

5.3 Carcinogenicity and mutagenicity

Epirubicin inhibits fertility in mice, is teratogenic, mutagenic, and carcinogenic. The drug causes immunosuppression by inhibiting the IgG response but does not affect cytotoxic immunity induced by T-cells, the predominant mechanism for antitumor immunity. Epirubicin is excreted in milk, due to its high protein binding.

6.0 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Epirubicin has a triexponential decline in plasma concentration after IV administration of doses ranging from 60-120 mg/m^2 in cancer patients. The initial half-life is approximately 3 minutes, the second is 2-3 hours, and the terminal half-life is 31-35 hours. Its pharmacokinetic profile is similar to that of doxorubicin, although the terminal half-life for doxorubicin is significantly longer (48 hours compared to 31 hours in Camaggi CM et al, Cancer Chemother. Pharmacol. 21: 221-8, 1988). The drug is extensively distributed throughout the body with a high volume of distribution, but it is cleared from tissues faster than doxorubicin. One author (Italia C et al, Br. J. Cancer 47: 545-547, 1983) found that epirubicin drug levels in muscle were lower than doxorubicin muscle levels, which might account for a reported decrease in cardiotoxicity with epirubicin. Its ability to cross the blood-brain barrier is moderate. Its pharmacokinetic profile is linear with increasing dose (60-150 mg/m^2). Systemic exposure to epirubicin is time-independent: clearance is not affected by duration of administration or by repeated doses with washout.

Epirubicin is highly protein bound and is lipophilic. Its clearance depends predominantly (60%) on biliary excretion and hepatic metabolism via two major pathways. Aldoketoreductases metabolize epirubicin to epirubicinol; this metabolite and the parent compound are also metabolized by glucuronosyl transferases. Doxorubicin

lacks a glucuronidation metabolic pathway. The two paths account for the higher elimination rate and shorter tissue retention of epirubicin compared to doxorubicin and may account for the reported decreased hematologic toxicity with epirubicin. Martini and colleagues (Int. J. Clin. Pharm. Res. IV 3: 231-238, 1984) found statistically significantly more hematologic toxicity in 8 breast cancer patients treated with doxorubicin compared to epirubicin in a cross-over study). Glucuronidation may lower the risk of cardiac toxicity relative to doxorubicin by removing toxic metabolites. Epirubicinol, the major metabolite, has cytotoxic activity, but its activity is 10-fold lower than that of epirubicin. The other metabolites have no appreciable antitumor activity. In addition to its significant hepatobiliary uptake, epirubicin is present in high concentrations in red blood cells, another site of metabolic activity.

Because the metabolic pathways for epirubicin involve P-450 reductases, but not the cytochrome P-450 isoenzymes, no major drug-drug interactions are expected. In the pivotal trials in this NDA, epirubicin was combined with cyclophosphamide and 5-fluorouracil (5-FU). The metabolic pathways differ for each of these drugs, making pharmacokinetic interactions unlikely. This hypothesis was confirmed by two clinical trials performed by the same investigators which evaluated epirubicin as a single agent or in combination with cyclophosphamide, 5-FU, and tamoxifen and found no change in the pharmacokinetic profiles (Jakobsen P et al. Cancer Chemother. Pharmacol 28: 465-9, 1991; Cancer Chemother. Pharmacol. 35: 45-52, 1991). Studies have not shown a change in the pharmacokinetic profile of epirubicin after paclitaxel or docetaxel administration (Conte PF et al, J. Clin. Oncol. 15: 2510-7, 1997; Esposito et al, 1998 in press: Rischin D et al, 1998 in press). Verapamil, given to reverse PGP-induced drug resistance, increased the amount of epirubicin metabolites, suggesting that coadministration increased the plasma clearance of epirubicin (Mross K et al, Cancer Chemother. Pharmacol. 31: 369-75, 1993). Dexrazoxane has not been shown to alter the pharmacokinetics of epirubicin (Basser RL et al, J. Clin. Oncol. 12: 1659-66, 1994; Jakobsen P et al, Cancer Chemother. Pharmaol. 35: 45-52, 1994).

Epirubicin pharmacokinetics are affected by certain conditions. Women have lower clearances than men; elderly women have lower clearances than young women. Patients with liver metastases have a 50% decrease in epirubicin clearance resulting in a higher systemic exposure. In this population, the volume of distribution decreased with no change in the terminal half-life. Clinical studies indicate that bilirubin and AST values are the best predictors of the need for a dose reduction in an individual patient. Because urinary clearance is a minor part of epirubicin excretion, dose reductions are not required for renal insufficiency.

7.0 Relevant Human Experience/Literature Review

Because epirubicin has been approved in many non-U.S. countries since 1982, the published literature is extensive. A PubMed search by the reviewer for all indications yielded 2003 articles. Five hundred fourteen articles on the use of epirubicin in breast cancer were identified. The sponsor submitted a review of the epirubicin literature, including search criteria to identify the articles relevant to this NDA. The literature will not be re-summarized in this review.

8.0 Early Breast Cancer: Study MA-5

Title: Cooperative clinical trial of intensive CEF versus standard CMF as adjuvant therapy for breast carcinoma in premenopausal patients with histologically involved axillary nodes.

Trial Accrual Dates: December 1, 1989 through July 1993
Data Lock Date: May 15, 1997
Cooperative Group: National Cancer Institute of Canada (NCIC)

8.1 Rationale and objectives

8.1.1 Rationale

Node positive breast cancer is associated with a 60% chance of relapse if treated with local measures only. Adjuvant therapy has resulted in a significant decrease in the chance of recurrence and mortality and has become the standard of care. However, many women still experience recurrence of their breast cancer, and newer therapies are needed to improve the outcome of this population.

The most commonly used adjuvant regimens include CMF and doxorubicin-based combinations. While many oncologists believe that doxorubicin is the most active agent in this setting, randomized trials of doxorubicin-based therapy compared to CMF have not conclusively demonstrated a survival benefit for anthracyclines. There is concern about the potential cardiac toxicity of these drugs. Epirubicin is an analogue of doxorubicin that has been reported to have less toxicity (both cardiac and hematologic) than and comparable efficacy to doxorubicin. Congestive heart failure (CHF) occurs in approximately 5% of patients who have received 450-550 mg/m^2; the sponsor states that a similar rate of cardiotoxicity was observed at cumulative epirubicin doses of 950-1000 mg/m^2. Trials also suggested that epirubicin was less myelosuppressive than doxorubicin. The original Phase I trials (1979-1980) with epirubicin established the optimal dose as 60 to 90 mg/m^2 when used as a single agent and as 50-75 mg/m^2 when used in combination. Subsequent studies demonstrated a dose-response relationship for anthracyclines, and a second set of Phase I trials (1983-1989) redefined the maximum tolerated dose (MTD) of epirubicin in combination at 100-150 mg/m^2.

Based on the data that indicated that epirubicin may be less toxic and equally effective as doxorubicin, and that its efficacy might be improved by increasing its dose-intensity, this clinical trial was designed to evaluate the efficacy and safety of "high-dose" epirubicin as part of the CEF regimen compared to CMF as therapy for early stage breast cancer.

8.1.2 Objectives

- To compare the duration of relapse-free survival and overall survival among premenopausal women with axillary node positive breast cancer following surgical resection of all known disease who are randomized to receive as adjuvant therapy either an intensive cyclophosphamide, epirubicin, 5-fluorouracil (CEF) regimen or a standard cyclophosphamide, methotrexate, 5-fluorouracil (CMF) regimen
- To estimate the rates of toxicities among the patients who receive either CEF or CMF as adjuvant therapy
- To compare the quality of life among patients who receive either CEF or CMF as adjuvant therapy

8.2 Design

8.2.1 Dose and schedule

This trial was a randomized non-blinded Phase III trial of CEF versus CMF in node positive breast cancer patients following definitive local surgical treatment. Section 8.3 describes the stratification factors for randomization. The study was conducted at 39 member sites of the NCIC. Patients were randomized to receive CEF or CMF in the following doses and schedule:

Arm 1: CEF

Cyclophosphamide	75 mg/m^2 PO D 1-14
Epirubicin	60 mg/m^2 IV D 1, 8
5-Fluorouracil	500 mg/m^2 IV D 1, 8

Arm 2: CMF

Cyclophosphamide	100 mg/m^2 PO D 1-14
Methotrexate	40 mg/m^2 IV D 1, 8
5-Fluorouracil	600 mg/m^2 IV D 1, 8

Cycles were repeated every 28 days, and a total of 6 cycles were given on each arm of the study. Patients were required to begin treatment within 10 weeks of diagnostic surgical biopsy. The protocol specified delivery of 6 cycles of therapy, even though treatment delays might result in a treatment period of greater than 6 months.

A pilot study was performed first (Ontario Clinical Oncology Group), in which it was decided to use the most active schedule for CMF (incorporating day 1 and day 8 therapy for M and F, with 2 weeks of oral cyclophosphamide). The CEF schedule was originally designed with the identical doses for C and F and the same schedule of administration. The epirubicin dose in this trial was 50 mg/m^2. However, 3 of 8 patients treated with CEF were admitted with febrile neutropenia. The investigators decided to lower the doses of C and F and to use the highest tolerable dose of anthracycline, the most active drug in the regimen, in order to maximize efficacy; the schedule was not altered. A Phase I dose-finding schema was used to identify optimal drug doses. At the

doses ultimately used in MA-5, the rate of febrile neutropenia was 18.8% (13 of 69 patients); the use of prophylactic antibiotics lowered the observed rate to 5% (3/60). In the pilot study, congestive heart failure (CHF) and significant drops in left ventricular ejection fraction (EF) as measured by radionuclide cardiac scan (MUGA) were not observed.

Based on these data, MA-5 was designed with the doses listed in the bulleted points above. Prophylactic Septra 2 tablets PO BID was used on the CEF arm only for the duration of therapy. Norfloxacin 400 mg PO BID or ciprofloxacin 500 mg PO BID was substituted in patients who could not tolerate Septra. Colony stimulating factors (CSF) were not used. Selective serotonin antagonist antiemetic drugs were not commonly available during the conduct of this trial. Per protocol, post-lumpectomy radiation therapy was deferred until chemotherapy was completed.

Reviewer Comments:

1. The trial was designed with the schedule and dose of CMF with the highest reported efficacy. The choice of the comparator is appropriate.

2. The rationale for the choice of CEF doses is sound.

3. If CEF is verified to improve survival compared to CMF in the adjuvant setting, the lower doses of C and F in the CEF combination provide support that the demonstrated efficacy is likely to be due predominantly to the effect of epirubicin.

4. Colony stimulating factors were not used in this trial. The use of CSFs might further reduce the incidence of neutropenia. There is no available information to compare the effects of prophylactic antibiotics with prophylactic CSF administration, or to evaluate the effects of combined prophylactic antibiotics with CSFs in the submitted trials. There is evidence in the published literature from other adjuvant trials that suggests a reduction in febrile neutropenia with combined therapy.

5. Selective serotonin antagonists were not available at the time this trial was conducted. The incidence of nausea and vomiting reported in this trial will be expected to be lower in current clinical practice.

8.2.2 Dose modifications

8.2.2.a Hematologic toxicity

Dose modifications were the same for both treatment arms. For hematologic toxicity, modifications for D1 administration were based on a combination of nadir and day 1 counts. Day 8 doses were re-evaluated based on D8 counts. Dose modifications for hematologic toxicity are summarized in the following tables:

Table 1. Dosing on D1 of the cycle (Sponsor's table a, volume 2.19, page 35)

Day 1 counts	Nadir	Dosing D1
AGC $\geq$ 1.5 x 10^9/L and platelets $\geq$ 100 x 10^9/L	AGC $\geq$ 0.2 x 10^9/L and platelets $\geq$ 50 x 10^9/L	100% of D1 of prior cycle
AGC $\geq$ 1.5 x 10^9/L and platelets $\geq$ 100 x 10^9/L	AGC < 0.2 x 10^9/L or platelets < 50 x 10^9/L or febrile neutropenia	Reduce to 75% of D1 of prior cycle
AGC < 1.5 x 10^9/L or platelets < 100 x 10^9/L	Any	Delay 1 week, then: (i) If AGC $\geq$ 1.5 x 10^9/L and platelets $\geq$ 100 x 10^9/L, dose adjusted based on nadirs (ii) If AGC 1 to 1.5 x 10^9/L and platelets $\geq$ 100 x 10^9/L, 75% of D1 of prior course given

Table 2. Dosing on D8 of the cycle (Sponsor's table b, volume 2.19, page 35)

Day 8 counts	Dose Adjustment
AGC $\geq$ 1.5 x 10^9/L and platelets $\geq$ 100 x 10^9/L	Same dose as on D1
AGC 1.0 x 10^9/L – 1.5 x 10^9/L and platelets $\geq$ 100 x 10^9/L	75% of D1 dose of the same cycle
AGC < 1.0 x 10^9/L or platelets < 100 x 10^9/L	No treatment. Start next cycle on D22 if counts permit

Once a D1 dose was reduced for hematologic toxicity, no dose re-escalation was permitted. If a D8 dose was reduced for hematologic toxicity, re-escalation on D1 of the subsequent cycle was permitted if blood counts were adequate.

Dose modifications refer to reductions in the doses of all 3 drugs.

8.2.2.b Non-hematologic toxicity

Some dose reductions were mandated for non-hematologic toxicity:

- Grade 3 mucositis: delay until recovery, then reduce all drugs by 25%
  - If grade 3 mucositis recurs at the lowered dose, give folinic acid
- No dose reductions for nausea
- Venous thromboembolic events: treat with heparin, followed by warfarin. Chemotherapy should be continued as planned; warfarin should be given for the duration of cytotoxic therapy
- Life-threatening arterial thrombotic events: remove patient from study
- Congestive heart failure on CEF: discontinue epirubicin and substitute methotrexate 40 mg/m^2
- Other intolerable toxicity: dose-reduce all drugs by 25% for 1 cycle and attempt to re-escalate

Reviewer Comments:

1. The guidelines for dose reductions were the same on each arm, and were the same for all drugs.

8.2.3 Baseline and follow-up evaluations

The schedule of evaluation is included in Appendix I. Patients were evaluated to rule out the presence of metastatic disease at baseline, were followed during chemotherapy, and were then followed at lengthening intervals for recurrence. Cardiac monitoring was performed at baseline and at 6, 12, 36, and 60 months. All patients were to be followed according to the schedule outlined in the protocol until recurrence or 10 years post-randomization, whichever occurred first. Patients were to be followed even if they discontinued therapy and even if they changed follow-up institutions. After 10 years of follow-up, minimal information on recurrence and death was required. All patients had to be followed until death.

Quality of life (QOL) evaluations were performed using an instrument designed for use by the NCIC in node positive breast cancer patients, the Breast Cancer Chemotherapy Questionnaire (BCCQ). The questionnaire was self-administered; the protocol stated the questionnaire should be completed prior to the administration of chemotherapy. Once treatment was finished, patients completed the questionnaire at each follow-up visit.

Reviewer Comment:

1. The schedule of follow-up visits is in accordance with accepted clinical practice. Because visits become less frequent, there is the potential to overestimate time to progression. This potential for bias should be the same on both treatment arms.

2. The questions on the QOL form do not address all of the side effects associated with CMF and CEF chemotherapy (for example, febrile neutropenia) and include some questions about unrelated effects (peripheral neuropathy).

3. The QOL forms were completed prior to chemotherapy, the accepted method of data collection.

4. The quality of the QOL life data will need to be evaluated. It will be important to identify how many patients did not complete a questionnaire at each timepoint, how much data was missing within each questionnaire, and whether the pattern of missing information was random or non-random. These issues are addressed in section 8.14, Quality of life.

8.3 Randomization and stratification

Randomization was performed centrally and was stratified by nodal status (1-3, 4-10, and >10 positive nodes), type of initial surgery (lumpectomy versus mastectomy), and by estrogen/progesterone receptor status (ER or PR $\geq$ 10, both < 10, or unknown status).

Reviewer Comments:

1. The randomization logs were provided. Patients were entered in chronological order at each site. Allocation to CMF or CEF was approximately equal by center.

2. One of the sites was the Hopital St.-Luc. Dr. Edgard Nassif was the principal investigator. In response to an FDA question, the sponsor noted that [redacted] was not

an investigator at this site. Twelve patients were entered at this site, or 1.7% of the study population.

3. Relapse and survival in early stage breast cancer are related to the number of involved lymph nodes; randomization was appropriately stratified for this important variable. The reviewer will examine these subgroups for safety and efficacy.

4. Randomization was not stratified by tumor size. This factor is less important than the number of positive nodes but may also affect outcome (predominantly for patients with T_{3-4} lesions). The reviewer will examine efficacy by tumor size as an exploratory analysis (section 8.12).

5. Other prognostic factors that are commonly used in current practice, such as proliferative indices, were not widely available at the time this study was conducted. These parameters are less important in node positive patients, where the number of positive nodes remains the primary determinant of prognosis.

8.4 Protocol amendments

The protocol was amended on May 17, 1990 and on October 18, 1990. The amendments were not detailed in the submission.

Reviewer Comments:

1. The sponsor was asked to provide the text of the amendments and the number of patients accrued at these timepoints.

May 17, 1990	The use of liver scan or liver CT was added to liver ultrasound for work-up of patients who presented with abnormal liver function tests (see Eligibility Criteria below; also added to baseline evaluation section)
	The use of ECHO was added for centers without cardiac radionuclide imaging capabilities
	Patients unable to complete QOL forms themselves were permitted to have assistance from an interpreter or family member
	Requirements for acceptable LFT parameters at baseline were added
	Cut-off times for baseline studies were added
	Specifications regarding dose re-escalation for D8 dose reductions were added

October 18, 1990 A BCCQ evaluation at 6 months was added

Folinic acid instead of a second dose reduction should be used for a second occurrence of grade 3 mucositis

2. These amendments should not have substantially changed the outcome of the trial.

8.5 Eligibility

8.5.1 Inclusion criteria

- Pre- or perimenopausal women
  - Defined as normal menstruation, amenorrhea for less than 1 year, biochemical evidence of ovarian function, amenorrhea for 1-3 years in patients younger than age 52, or hysterectomy without bilateral oophorectomy in patients younger than age 56
- Potentially curable adenocarcinoma of the breast, treated with either modified radical mastectomy or with lumpectomy and axillary node dissection, with radiation planned after the completion of chemotherapy
- One or more positive axillary lymph nodes
- Must be clinical stage $T_{0\text{-}3a}$ $N_{0\text{-}2}$ M_0 prior to surgery
  - Patients with T_4 tumors or M_1 disease are not eligible
- Pathologic stage $T_{0\text{-}4}$ $N_{1\text{-}2}$ M_0 following surgery
  - Patients with dermal lymphatic invasion (T_4) found only on pathology review, without clinical signs, are eligible
- Negative work-up for metastatic disease (chest X-ray, bone scan; liver imaging only in the presence of elevated liver function tests)
- Baseline cardiac scan (ECHO only if the center does not have nuclear medicine testing available) with LVEF $\geq$ 45%. The same technique used to evaluate cardiac status at baseline must be used at each subsequent evaluation.
- Bilateral breast cancer patients are eligible. Tumor characteristics on 1 side must meet the above criteria. Both sides must have been completely resected, but axillary nodal dissection (AND) is optional on one side if the axilla is clinically negative.
- Must be randomized and start treatment within 10 weeks of first surgical diagnostic evidence of breast cancer
- Must be willing to participate with protocol requirements

Reviewer Comments:

1. Postmenopausal women were excluded. This trial does not support a labeling claim in this group of women.

2. A prospective definition of premenopausal versus perimenopausal was not provided. The sponsor was asked about this issue; Pharmacia & Upjohn noted that premenopausal was defined as the presence of normal menstruation; perimenopausal status was defined by the other criteria listed above.

3. Radiation was given at the conclusion of therapy. In the recent literature, delay in local radiation therapy has been reported to increase the risk of local recurrence, but immediate chemotherapy decreases the chance of systemic recurrence. It will be interesting to evaluate local recurrence rates in this trial (see section 8.12, Efficacy).

4. Patients with dermal lymphatic invasion, even in the absence of the clinical diagnosis of inflammatory breast cancer, have a poorer outcome than a node positive patient without this finding. This information was not included in the database. The sponsor was asked about this issue. In order to answer this question, each pathology report would need to be manually retrieved and reviewed.

5. ECHO is generally considered to be inferior to nuclear medicine scans in the accuracy of LVEF determination. The database did not note which test was used to measure cardiac function.

7. Abdominal ultrasound and a liver/spleen scan are not as accurate as abdominal CT in evaluating the presence of hepatic metastases. Forty-seven patients on each arm presented with at least one elevated liver function test value. None of these patients were evaluated with abdominal CT. The evaluation of these patients is presented in the following table:

Table 3. Diagnostic work-up of patients who presented with abnormal LFTs

Test/Result	CEF	CMF
Abnormal baseline LFTs	**47**	**47**
No evaluation	10	6
Ultrasound/normal	17	24
Ultrasound/abnormal	5	3
Liver scan/normal	12	11
Liver scan/abnormal	0	0
"Normal"	3	2
Unknown	0	1

It is not possible to evaluate the consistency of the test modality used for follow-up, as the database includes one category for hepatic evaluation. The patients with abnormal hepatic ultrasounds were entered on study; the nature of the abnormality was not provided in the application. Four women on CEF with baseline abnormal liver function tests and 3 on CMF relapsed in less than 1 year. Only 1 patient, LC004, had an abnormal hepatic imaging study.

Overall, the small numbers of patients involved and the approximately equal distribution of these patients between treatment arms should not significantly affect the outcome of the study.

8. Inclusion of women with bilateral breast cancer is acceptable, provided that both cancers are fully staged and that inclusion/exclusion is based on the worst prognosis tumor seen. Axillary examination is an inaccurate tool for assessment of the axilla; experienced clinicians are incorrect 30% of the time. Because this trial was designed to capture women with positive lymph nodes, it is unlikely that an undissected axillary that was histologically negative would influence the outcome of the trial. However, if the undissected axilla contained positive nodes, the number of occult positive nodes might imbalance the treatment arms. This information was not included in the database. The

sponsor answered that all patient charts would need to be reviewed to determine how many patients had bilateral disease, how many had bilateral node dissections, and the staging of each side. The impression of the NCIC-CTG investigators was that less than 5 patients with bilateral disease were entered on study.

8.5.2 Exclusion criteria

- Residual tumor in the axilla following dissection
- Microscopic evidence of residual tumor at the resection margins of a mastectomy
  - Patients with microscopic residual disease after lumpectomy are highly recommended to undergo re-excision. If not performed, patients are still eligible provided that a boost to the tumor bed is given along with the planned post-lumpectomy radiation therapy
- Use of regional nodal or post-mastectomy chest wall irradiation
- Tamoxifen, prednisone, other hormonal/cytotoxic therapy other than the planned regimen
- Metastatic disease beyond the homolateral axillary nodes
- Prior or concurrent neoplasm other than basal cell or squamous cell skin carcinoma or cancer of the cervix, endometrium, colon, or thyroid treated more than 5 years prior to study entry and presumed cured
- Any prior therapy for breast cancer
- History of cardiac disease (angina, documented MI, existing cardiac failure)
- Serious underlying medical illness or psychiatric/addictive disorder
- Inadequate hematologic, renal, hepatic function (defined in the protocol)

Reviewer Comments:

1. The exclusion criteria are appropriate.

2. The amount of residual tumor after lumpectomy, without a re-excision, might influence local recurrence rates and potentially distant recurrence rates. This information was not entered in the database; the sponsor indicated that manual review of all pathology reports would be necessary to answer the question.

3. Tamoxifen use was not permitted on this study. According to a MS Access query of the database, 70 patients on CMF and 59 on CEF took hormone therapy. This imbalance potentially favors CMF.

8.6 Endpoints

Progression was defined as local, regional, or distant:

- Local breast recurrence: recurrence within the breast following partial mastectomy
- Local chest wall recurrence: recurrent cutaneous or subcutaneous tumor occurring in an area bounded superiorly by the clavicle, inferiorly by a horizontal line at the level of the xiphisternum, medially by the midline, and laterally by the posterior axillary line

- Regional nodal recurrence: recurrent tumor in the lymph nodes in the homolateral axilla, homolateral supraclavicular fossa, or ipsilateral internal mammary chain
- Distant recurrence: spread of disease beyond the limits specified for regional recurrence
- Contralateral breast cancer: considered a second primary, not a recurrence

The determination of local-regional progression was considered definite if based on a positive cytology, aspiration, or biopsy. It was considered suspicious if based on a visible or palpable lesion.

The following evidence was required for distant recurrence:

- Bone marrow
  - Definite: positive cytology, aspiration, or biopsy
  - Suspicious: leukoerythroblastic blood picture
- Lungs and pleura
  - Definite: positive cytology, aspiration, or biopsy, or presence of multiple pulmonary nodules felt to be consistent with pulmonary metastases
  - Solitary lesions require further work-up
- Skeletal
  - Definite: X-ray evidence of lytic, blastic, or mixed lesions on skeletal films with or without bone scan confirmation
  - Biopsy proof of bone metastases
  - Progressive bone scan changes over at least a 4 week period showing development of new lesions is necessary in asymptomatic patients with only bone scan abnormalities
  - In the absence of progressive disease by scan, a biopsy is strongly recommended. A scan positive in joints or in a recent area of trauma cannot be used as a criterion of treatment failure.
- Ascites or pleural effusions
  - Definite: positive cytology
  - Suspicious: roentgenographic or clinical evidence
- Liver
  - Definite: liver enlargement (especially if nodular) with additional confirmation by an abnormal liver scan, ultrasound, or CT scan demonstrating solid space-occupying lesions OR liver biopsy confirmation of metastatic disease
  - If radiographic findings are not definitive, a liver biopsy is mandatory.
- Central nervous system
  - Definite: positive CT scan, usually in a patient with neurologic symptoms, or a positive biopsy or cytology
- Contralateral breast cancer: considered as a second primary malignancy

The progression date could be based on a sign but not on a symptom. The date of first detection of a palpable lesion was acceptable only if tumor diagnosis was subsequently established. The date of the first positive X-ray should be used, even if determined retrospectively.

All patients were to be followed until death. Postmortem examinations were strongly encouraged in cases where the cause of death could not be clearly assigned.

Reviewer Comment:

1. Relapse-free survival can be difficult to determine and is subject to bias. In this trial, survival information is available and provides the best evidence of efficacy.

2. The sponsor appropriately considers a contralateral breast cancer to represent a new primary and not a recurrence. As indicated below, patients were not considered to have relapsed when diagnosed with a contralateral breast cancer.

3. Patients with an in-breast recurrence after lumpectomy should be analyzed separately from those patients with chest wall recurrence after mastectomy or distant recurrence. At least seven prospective randomized trials have shown that survival is the same with lumpectomy and radiation therapy compared to modified radical mastectomy, despite a higher local recurrence rate in women who undergo conservative surgery. These data suggest that recurrence in the breast does not convey the same poor prognosis as chest wall recurrence. An analysis of all recurrences of any type as well as analyses of women with chest wall/distant recurrence and of women with in-breast recurrence would be helpful.

8.7 Statistical Plan

8.7.1 Prospectively Defined

The primary response variable was disease-free survival (DFS), defined as the time from randomization until recurrence of disease as defined in section 8.6, Endpoints.

The secondary endpoints were overall survival (OS), toxicity rate, and quality of life. Survival was defined as the time from randomization until death from any cause. The toxicity rate was defined as the incidence of events estimated as possibly, probably, or definitely due to protocol therapy by Common Toxicity Criteria (CTC; older version). Quality of life was based on the BCCQ.

The primary analysis was planned as a comparison of relapse-free survival (RFS) between the two treatment groups as described by the Life Table Method and compared by the Mantel-Haenszel test. A patient who died of an unrelated cause was to be censored as event-free at the time of death. The secondary analysis of survival was planned with the same methods, using all deaths, both breast cancer- and non-breast cancer-related.

The Cox proportional hazard model was specified to assess the effect of treatment groups and the effects of prognostic variables on outcome.

Toxicity and QOL were to be analyzed by repeated measures analysis of variance. Safety analyses were to be performed according to actual, rather than randomized, treatment.

The sample size was calculated using a one-sided alpha, because demonstrating that CEF is inferior to CMF was not of interest. [Reviewer note: All analyses were, however, conducted with a two-sided alpha]. A series of calculations were made using different estimates of 5-year RFS in the CEF and CMF groups, ranging from 45-65% for CMF and from 55-75% for CEF. A sample size of 296 patients per group was estimated to provide a 10% improvement in DFS after 5 years of follow-up, with 118 observed

events in each group. Another method of calculation was used to estimate that enrollment of 600 patients in a 4-year time frame, with an additional 3 years of follow-up, was sufficient to demonstrate a difference in median DFS from 5.8 years for CMF to 8.1 years for CEF with 80% power (one-sided alpha of 0.05). These median DFS times were considered equivalent to 55% and 65% 5-year DFS respectively.

No interim analyses were planned. However, death rates were monitored on the combined groups in order to revise the sample size if the assumptions were inaccurate. No such revision was performed.

For the QOL evaluations, a change of 0.5 on the BCCQ was deemed clinically significant. Fifty patients would be needed to detect this difference; the projected sample size of 600 patients was large enough to identify a difference. The two groups were to be compared using an analysis of variance with repeated measures. A growth curve analysis was specified to model the data on quality of life and compare groups over time.

Reviewer Comments:

1. The prognostic variables entered in the Cox proportional hazards model were not prospectively specified.

2. The BCCQ was scored by adding together the scores from each of the 30 questions (scored on a 7-point scale) and determining the mean. From the listed answers, it does not appear that a change of 0.5 represents a clinically meaningful difference. A score of 2 is given for "most of the time" or " a little of the time" or "a lot of trouble". A score of 3 is given for "a good bit of the time", "some of the time", or "a fair bit of trouble." Patients who answered all questions with 2s and subsequently answered with all 3s have a difference of 1.0 in mean scores. Because of the similarity of the answers, it is unlikely that this difference represents a meaningful improvement in their quality of life.

3. Using the mean weights all questions equally. The question "How often during the past four weeks have you felt your fingers were numb or falling asleep?" does not describe side effects related to the chemotherapy in the study. It is given equal importance as a question about the occurrence of mouth sores, which was a common adverse event in this trial. Some questions were asked two to four times: patients were asked about their concerns about hair loss 3 times, about fatigue 4 times, about nausea/vomiting twice, and about their level of optimism and positive thinking twice. The question "How much trouble or inconvenience have you had during the last four weeks as a result of waiting for treatment at the clinic or hospital?" was asked 4 times. The use of repetitive questions may be designed to assign greater significance to one effect compared to another, but the validity of the weighting system is not known.

8.7.2 As defined in the study report

The study report described a statistical plan that was more precise and detailed than that defined in the protocol. The additions and amplifications are described below.

8.7.2.a Populations to be analyzed

The first analysis was performed after 3 years of follow-up, when recruitment was complete and 263 events had occurred.

Two sets of analyses were performed:

- All registered and randomized patients
  - No patient was registered but not randomized
  - Analysis included all patients, regardless of whether they received the randomized therapy, whether or not they were treated, or whether or not they were eligible—Intent-to-treat analysis
- Patients as treated
  - Included only those patients who received therapy, and analyzed them according to received, not randomized, treatment

8.7.2.b Analysis of RFS

A patient who died of an unrelated cause was censored as event-free at the time of death per protocol; the study report stated that patients with contralateral breast cancer or a second primary malignancy were also censored in this analysis.

Frequency of relapse was reported by the stratification features, menopausal status (pre- versus perimenopausal), and tumor size, now identified as "prognostic features".

The primary analysis was now specified as comparison by the stratified log-rank test. Kaplan-Meier curves of RFS were generated for the entire group of randomized patients and by each prognostic factor. The RFS at 5 years and the 25th percentiles of the probability distribution of relapse (75% RFS with interpolated values) were presented.

A Cox proportional hazards model was used to evaluate the effect of the number of positive nodes, receptor status, type of surgery, menopausal status, and tumor size. Each factor was assessed individually, then a forward stepwise procedure was used to select the factors to be included in the model. A significance level of 0.05 was used. An extended model including first-degree interactions between the factor and treatment was applied and the goodness of fit of the model was tested. The negative of twice the difference between the log likelihood for this model and the model without the interaction were compared against a chi-squared distribution with degrees of freedom (DF) equal to the sum of DF of the interactions. Cases with missing data for any of the covariates were removed from the data set when the model was fit. The class of unknown receptor status was excluded from the analysis also.

8.7.2.c Grouped intervals for assessing the risk of death

The frequency of death was summarized for the ITT population and for subgroups of patients based on the prognostic factors.

The number of patients at risk for death were grouped by treatment start, at 6 months, and at 1, 3, and 5 years.

8.7.2.d Patient characteristics

The protocol specified characteristics to be collected. The study report stated that age, menopausal status, performance status (PS), type of surgery, number of evaluated and positive nodes, ER/PR status, and clinical TNM staging of disease were summarized in frequency tables and analyzed with descriptive statistics. The distribution of patients with normal or abnormal findings for EF was also summarized. The intent-to-treat population was used.

8.7.2.e Actual and relative dose-intensity

Dose-intensity (DI) was defined as the actual weekly dose delivered in mg/m^2/wk (actual DI) and as the ratio between the weekly actual dose and the weekly dose specified in the protocol (relative DI). A fixed interval of 4 weeks was added to compute the length of the last cycle. Descriptive statistics and the upper and lower quartiles of distribution were used to display these results. The actual and relative DIs were calculated for patients who did and did not receive radiotherapy as specified in the protocol. The cumulative doses of epirubicin and methotrexate for the two groups were compared.

8.7.2.f Extent of exposure

Extent of exposure was summarized by a frequency table based on the maximum number of completed cycles in as-treated patients and by descriptive statistics. A cycle was defined as completed if the study drug was delivered at least once during that cycle. The actual and relative durations of each cycle and all cycles were calculated. The actual duration of a cycle was calculated as the difference in the starting dates of two consecutive cycles; the 6th cycle was excluded from analysis. The frequency of delayed cycles and the extent of the delay were calculated. Cycles were delayed if the interval was greater than 28 days. Day 8 therapy was considered delayed if the interval was greater than 7 days. A chi-square test was used to test for differences between the two treatment groups.

8.7.2.g Radiotherapy

The frequency of as-treated patients who received radiation therapy was summarized by whether it was given prior to the last dose of chemotherapy or after the last dose of chemotherapy.

8.7.2.h Quality of life

The BCCQ was used to evaluate QOL. According to the study report, the original questionnaire contained 30 questions. Two additional questions were added during the study. The QOL summary score was calculated as the mean of the scores on all 30 original questions, each of which was answered on a 7-point Likert scale. The lowest score always represented the worst possible outcome and the highest score the best possible outcome. For items 2 and 9, the responses were inverted by subtracting the given score from 8 in order to conform to this convention.

The sponsor stated in volume 2.19, page 49 that the protocol called for an analysis only for patients who provided complete answers to all questions. The reviewer was unable to find that reference in the original protocol. A new procedure for analysis, including strategies for handling missing data, was written.

8.7.2.i Adverse events

Adverse events were summarized according to the number and percentage of patients with an event, categorized by body system and event. If a patient experienced the event more than once, the worst grade attained was presented. Events were also presented by cycle.

Adverse events that occurred during radiotherapy, given after chemotherapy, were not included in the analysis.

The number and percentage of patients who died, withdrew from study because of adverse events, or who withdrew because of a non-fatal serious adverse event were reported by cycle.

The frequency of deaths was reported by cause and whether it occurred on treatment or after discontinuation of study drugs.

Descriptive statistics were used to describe laboratory values, using the worst grade attained during a cycle, and the difference in grade between the most severe value recorded during treatment compared to baseline.

Changes in LVEF were evaluated between the 6-month assessment and baseline. Values less than 45% were considered abnormal (the local ranges for normal were not collected). Changes over time were presented. Listings of patients with drops in LVEF either below 45% or with drops of 20% relative to baseline were generated.

Reviewer Comments:

1. The statistical analysis differed from that defined in the protocol. The medical reviewer discussed the differences with the statistical reviewer. The Mantel-Haenszel test is comparable to the logrank test; the primary analysis plan is sufficiently similar in the protocol and the study report. Further comments about the statistical methodology can be found in Dr. Davi's review.

2. It is acceptable to perform an "as-treated" analysis in order to obtain a more accurate assessment of toxicity. The intent-to-treat analysis is considered the primary efficacy analysis by the division.

3. The first analysis at 3 years of follow-up was specified as the primary analysis by the protocol. The current analysis provides longer follow-up which is critical in assessing the efficacy of this therapy in early stage breast cancer, because of the long natural history of this illness.

4. The prognostic factors for the Cox model were not specified in the protocol. The unadjusted analysis is the primary analysis; use of a model may generate new hypotheses for future trials or provide additional support for the robustness of the data. The use of the stratification factors for randomization is acceptable. Tumor size is a recognized prognostic factor for breast cancer and these data were prospectively collected; it is appropriate, from a clinical perspective, to include this factor. The use of pre- versus perimenopausal status in this model is questionable. There was no prospective definition of premenopausal compared to postmenopausal. Published literature indicates that these women respond similarly to chemotherapy and both may respond differently than postmenopausal women. The clinical relevance of this distinction is not clear. The reviewer will ask Dr. Davi to repeat the Cox modeling without this variable.

5. Patients at risk for death may be grouped in time intervals as described by the sponsor. These groups correspond to the duration of treatment and the most common intervals for considering relapse/death in breast cancer. However, an overall analysis, without predefined cut points, should also be performed.

6. The study report (volume 2.19, pages 40-41) outlined factors used to identify patient characteristics and included statistical plans to analyze dose-intensity, duration of

drug exposure, timing of radiotherapy, and adverse events. While not prospectively defined in the protocol, these factors were prospectively collected and analyzed by descriptive statistics. These analyses do not change the outcome of the primary efficacy variables and are unlikely to be subject to bias.

7. There was no formal statistical plan for analyzing cardiotoxicity. The CRF prospectively collected information on the MUGA/ECHO results; copies of all reports were required submissions. The definition of cardiotoxicity using LVEF changes was not made prospectively. However, this definition has been used by other sponsors in the development of other cardiotoxic and cardioprotective (e.g., Zinecard) agents and is acceptable. The most informative analysis is probably not a comparison of baseline and 6 month values, but a comparison of baseline and subsequent timepoints, since anthracycline-induced cardiac toxicity is usually delayed.

8. No clear plan for analysis of QOL data was generated until after the study was completed. The analysis and its potential limitations will be discussed with the statistical reviewer, Dr. Davi.

9. Although the study report indicates that two questions were added to the BCCQ during the course of the study, answers for 30 questions, not 32, were provided in the database.

8.8 Enrollment and demographics

8.8.1 Enrollment

A total of 716 women were accrued and randomized on this trial. The sample size calculations specified enrollment of 600 women, but additional patients were entered due to the rapid accrual rate and the lack of a replacement adjuvant trial within the cooperative group. Three hundred fifty-six women were randomized to receive CEF and 360 were randomized to receive CMF.

Two patients (KO006, randomized to CEF, and LM055, randomized to CMF) were not treated. Both patients were ineligible because greater than 10 weeks had passed since primary surgery.

Several patients did not receive the randomized treatment regimen. Patient PN001 was randomized to CEF but received methotrexate instead of epirubicin for all 6 cycles (refused CEF treatment). In the as-treated analysis, this patient was included in the CMF arm. Patient LM008 received methotrexate instead of epirubicin on Day 1, Cycle 5. Patient LY009 received methotrexate instead of epirubicin for cycles 2-6. In the as-treated analysis, both patients were included in the CEF group.

Table 4. Patient population for efficacy and safety analyses (Volume 2.19, Sponsor's table 1, page 55 and sponsor's table 1.1, page 95)

Patient population	CEF	CMF	Total
Total randomized (used in all efficacy analyses)	356	360	716
Never treated	1	1	2
Total treated	355	359	714
Treated with non-randomized arm	1	0	1
Treated with randomized arm	354	359	713
Safety population: As-treated	354	360*	714

*Includes 1 patient randomized to CEF treated with CMF instead

Reviewer Comment:

1. Two of 716 randomized patients (0.3%), one on each arm, did not receive therapy. This number is low and should not influence study outcome.

2. Three of 716 randomized patients (0.4%) received the incorrect therapy. This number is low and should not influence study outcome. Since all of the patients were randomized to CEF and received varying amounts of CMF instead, the only effect might be to diminish the observed effect of the CEF regimen. Also, this small number ensures that the intent-to-treat analyses will be similar to the as-treated analyses.

3. The patients who did not receive treatment and the patients who did not receive the randomized therapy (5 total) were distributed among 4 sites. There is no evidence of site-specific treatment bias.

8.8.2 Demographics

Patient demographic factors are summarized in the following table:

Table 5. Demographic characteristics at baseline (ITT) (Sponsor's table 4, volume 2.19, page 58)

Variable		CEF (n= 356)	CMF (n=360)
Age (years)	Median (range)	44.5 (25.8-55.7)	44.5 (23.4-57.2)
	Mean ± SD	43.8 ± 5.9	44.0 ± 6.1
No. patients distributed by age	≤ 29	4 (1%)	6 (2%)
	30-39	87 (24%)	77 (21%)
	40-49	209 (59%)	216 (60%)
	50-59	56 (16%)	61 (17%)
ECOG PS	Median (range)	0 (0-2)	0 (0-2)
	0	279 (78)	298 (83)
	1	74 (21)	60 (17)
	2	2 (1)	2 (1)
	Missing	1 (0%)	0 (0%)
Menopausal status	Premenopausal	276 (78%)	285 (79%)
	Perimenopausal	80 (22%)	75 (21%)

These factors were similar between the two treatment groups.

The following table summarizes the baseline stratification variables and tumor characteristics:

Table 6. Pretreatment prognostic and stratification factors (Sponsor's table 5, volume 2.19, page 59)

Variable		No. of patients (%)	
		CEF (n=356)	CMF (n=360)
No. nodes examined	1-5	28 (8)	31 (9)
	6-10	128 (36)	136 (38)
	>10	200 (56)	193 (54)
No. positive nodes	1-3	218 (61)	218 (61)
	4-10	115 (32)	118 (33)
	>10	23 (6)	24 (7)
ER status	Negative (<10)	103 (29)	98 (27)
	Positive (≥ 10)	213 (60)	215 (60)
	Unknown	40 (11)	47 (13)
PR status	Negative (< 10)	89 (25)	99 (28)
	Positive (≥ 10)	225 (63)	212 (59)
	Unknown	42 (12)	49 (14)
Clinical stage	I	135 (38)	144 (40)
	II	178 (50)	174 (48)
	III	14 (4)	22 (6)
	Unknown	29 (8)	20 (6)
T-clinical	0	11 (3)	8 (2)
	1	148 (42)	154 (43)
	2	151 (42)	152 (42)
	2A	1 (0)	1 (0)
	3	13 (4)	22 (6)
	3A	1 (0)	0 (0)
	X	22 (6)	20 (6)
N-clinical	0	269 (76)	280 (78)
	1	76 (21)	69 (19)
	2	1 (0)	3 (1)
	Unknown	10 (3)	8 (2)
Surgery	Partial mastectomy	175 (49%)	176 (49%)
	Total mastectomy	181 (51%)	184 (51%)

The sponsor indicates that these characteristics were well-balanced between arms. The majority of patients had 1-3 involved lymph nodes and were ER and PR positive. The type of local treatment was evenly distributed in the entire population and between treatment groups.

All patients had normal LVEF values at baseline.

Per protocol, radiation therapy was to be administered after the completion of chemotherapy. On the CEF arm, 192 patients did not receive any radiotherapy; 160 received it after chemotherapy; and 2 received it during chemotherapy. Two patients had post-mastectomy chest wall irradiation, which was prohibited by the protocol. On the CMF arm, 191 patients did not receive radiotherapy; 164 received radiotherapy after chemotherapy; and 4 received it during chemotherapy.

Reviewer Comment:

1. The reviewer agrees that treatment characteristics were equally distributed between treatment arms.

2. A clinical difference between pre- and perimenopausal breast cancer has not been established.

3. Of interest, approximately 40% of women on each arm were clinically Stage I. This finding is in keeping with the reported level of inaccuracy of physical examination in determining axillary involvement with breast cancer.

4. Four and six percent of CEF and CMF patients respectively presented with clinical Stage III disease (T_3 tumors). The small number of stage III patients was equally distributed between treatment arms and should not affect the study results.

After surgery, 43 women on CMF and 25 on CEF had pathologic evidence of T_3 tumors (7% and 12% respectively). All had N_1 disease pathologically except for 2 patients randomized to CMF, who had N_2 disease. One patient on each arm had pathologic evidence of a T_4 lesion.

5. Two women on CEF and none on CMF received postmastectomy chest wall irradiation. Although recent reports have demonstrated a survival benefit for postmastectomy chest wall irradiation in node positive women, the small number of affected women in this study is unlikely to bias the results.

6. From the numbers cited for radiotherapy, 13 patients treated with partial mastectomy on the CEF arm did not receive radiation therapy at any time. On the CMF arm, 191 patients did not receive radiotherapy. The study report states that 168 patients received radiotherapy. Patients treated with a total mastectomy (184) should not have received radiation, suggesting that 7 patients on the partial mastectomy arm did not receive radiation therapy. However, there were 176 patients treated with a partial mastectomy; all of these patients should have received radiotherapy. Based on this information, either 7 or 8 lumpectomy patients did not receive radiation. The database shows that 2 patients on CEF and 2 on CMF underwent lumpectomy but did not receive radiation. One patient on CEF, patient SA11, died of a cerebral hemorrhage during chemotherapy. The second patient on CEF was alive and disease-free at last follow-up; the reason for not administering radiation is not documented in the electronic database. Two patients on CMF (MR6 and LM4) relapsed close to the end of the planned chemotherapy and did not receive breast radiation. The reasons for omitting radiotherapy in the remaining patients are unclear.

8.9 On-study follow-up

The following table summarizes the disposition of the patients over time:

Table 7. Patient disposition (intent-to-treat) (Sponsor's table 2, volume 2.19, page 55)

Time Interval	CEF (n=356)		CMF (n=360)	
	No. pts (%) completing	No. pts (%) withdrawn*	No. pts (%) completing	No. pts (%) withdrawn*
Registration	356 (100)	0 (0)	360 (100)	0 (0)
Treatment start	355 (100)	1 (<1)	359 (100)	1 (<1)
6 month F/U	351 (99)	2 (1)	359 (100)	0 (0)
1 year F/U	348 (98)	3 (1)	355 (99)	4 (1)
3 year F/U	299 (84)	46 (13)	289 (80)	60 (17)
5 year F/U	119 (33)	26 (7)	121 (34)	37 (10)
> 5 years (analysis cut-off date)	108 (30)	11 (3)	115 (32)	6 (2)
Median F/U months (range)	54 (0-84)		54 (0-84)	
Patients not treated	1		1	
Patients receiving wrong treatment	1		0	

* Includes lost to follow-up, withdrawal because of toxicity, patient refusal, death from any cause. Excludes censored patients who are not considered withdrawn from any given interval, but have not completed each of the time intervals up to 5 years.

Similar numbers of patients in each group were followed at each time point. The median follow-up was similar in each treatment group.

Reviewer Comments:

1. A similar number of patients completed each segment of therapy and follow-up. Figure 1.3, volume 2.19, page 169 confirms that the duration of follow-up and the percentage of patients followed was virtually identical between treatment arms.

8.10 Removal from study, protocol violations

8.10.1 Removal from study

Patients were to be removed from study for the following reasons:

- Intercurrent illness which would, in the opinion of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of a drug
- Unacceptable toxicity (defined in the protocol)
- Disease recurrence; however, these patients will be followed until death
- Patient request; every effort should be made to continue to follow these patients
- Life-threatening arterial thrombotic events

Patients were not removed from study for:

- Diagnosis of a second primary during adjuvant chemotherapy
- Local breast recurrence

Eight patients stopped therapy due to toxicity, 6 on CEF and 2 on CMF. The CEF patients discontinued therapy for nausea and skin rash; fever/cold; cerebrovascular accident; febrile neutropenia and GI pain; proctitis and mucositis; and 1 patient because of lethargy, diarrhea, nausea, vomiting, stomatitis, mood problem, alopecia, local toxicity, skin rash, and other GI problems. On CMF, one patient discontinued therapy because of memory loss and one discontinued therapy because of lethargy, hot flashes, diarrhea, nausea, other GI problems, conjunctivitis, and cough.

Reviewer Comments:

1. The development of a new breast cancer during active treatment indicates a drug-resistant tumor. These tumors might be expected to be highly aggressive, and outcome in these patients may be more reflective of the new cancer than of the therapy used to treat the initial cancer. In reviewing the database and narratives, 8 women on CEF and 9 on CMF developed new breast primaries. One case on CEF and 2 on CMF were ductal carcinomas in situ. There was no apparent difference in outcome between the two groups and no evidence of highly aggressive malignancy.

8.10.2 Protocol violations

The planned sample size was 600 patients, but 716 patients were accrued due to a higher than expected accrual rate.

In the CEF group, 21 of 356 patients (6%) and 24 of 360 patients (7%) had at least one protocol violation. The following table summarizes the violations:

Table 8. Summary of protocol deviations on study (Sponsor's table 2.1, volume 2.19, page 99)

Deviations	CEF N=356	CMF N=360	Total N=716
None	335 (94%)	336 (93%)	671 (94%)
At least one:			
Pathology section margins positive	2 (1%)	0	2 (0%)
Clinical stage M1	1 (0%)	0	1(0%)
Randomized >10 wks post-surgery	1 (0%)	1 (0%)	2 (0%)
Contraindicated treatment	1 (0%)	0	1 (0%)
Quality of life	2 (1%)	4 (1%)	6 (1%)
Therapeutic: modification	1 (0%)	1 (0%)	2 (0%)
Therapeutic: regimen	14 (4%)	20 (6%)	34 (5%)

Two patients on CEF and 4 on CMF had radiation therapy performed during chemotherapy, a protocol violation. Two patients on CEF received post-mastectomy chest wall irradiation.

Reviewer Comments:

1. Overall, few patients had protocol deviations. Most were balanced between arms. Major violations, such as the presence of metastatic disease and persistently positive margins, occurred more often on the CEF arm than the CMF arm.

2. Few patients received radiation during chemotherapy or received postmastectomy chest wall irradiation. This violation, because of the small numbers of patients involved, is unlikely to significantly affect the study outcome.

3. Review of the narratives indicated that one patient randomized to CEF received doxorubicin instead of epirubicin during one cycle.

4. Review of the 3-year report documents that 22 patients received hormonal therapy while on study, 1 patient received prednisone therapy, and 1 patient was given G-CSF (volume 2.26, page 8/17/196). The treatment assignment of these patients was not given. A MS Access query of the submitted database indicates that 70 patients on CMF and 59 on CEF received hormonal therapy.

5. As mentioned previously, ten patients on CEF and 6 on CMF were entered on study with abnormal liver function tests and without hepatic imaging.

6. Patient MV4, randomized to CMF, received radiation therapy prior to chemotherapy.

7. The sponsor was asked for the definitions of "Quality of life", "Therapeutic: modification", and "Therapeutic: regimen". Quality of life protocol violations described failure to complete the required QOL questionnaire. "Therapeutic: modification" refers to deviations from protocol-prescribed dose-reductions for toxicity so extreme that it is questionable whether the patient could be said to receive the "protocol specified treatment." Examples included discontinuation of a major component of a regimen for reasons other than those specified in the protocol, substantial uncalled for dose reductions, and no dose reductions when required in the protocol. "Therapeutic: regimen" referred to the use of a treatment regimen other than that to which the patient was randomized. Examples of these violations included patients who did not receive any of the allocated therapy, patients who received alternate therapy, patients who did not complete treatment for reasons other than those specified in the protocol, patients who received additional treatment that interfered with the evaluability of a major endpoint, incomplete surgery, or gross error in radiotherapy fields.

8.11 On-study treatment

8.11.1 Discontinuation of chemotherapy

Per protocol, 6 cycles of chemotherapy were to be administered unless there was disease progression, toxicity, or patient refusal. The reasons for discontinuing drug therapy are listed below.

Table 9. Reasons for treatment discontinuation (as-treated analysis) (Sponsor's table 3, volume 2.19, page 56)

	No. Patients (%)	
	CEF (n= 354)	CMF (n=360)
Total early treatment discontinuations	**13 (4)**	**10 (3)**
Reason for withdrawal		
Toxicity	6 (2)	2 (1)
Refused treatment	4 (1)	4 (1)
Progressive disease	0 (0)	2 (1)
Death	1 (<1)	0 (0)
Other	1 (<1)	2 (1)
Missing	1 (<1)	0 (0)

Few patients discontinued or refused to complete planned study therapy. The number of patients who did not complete 6 cycles of therapy is similar between the two arms, as are the reasons for treatment discontinuation.

Reviewer Comment:

1. Overall, a small percentage of patients did not complete the planned course of adjuvant therapy. As presented here, toxicity and patient acceptance of the treatment were similar between the two arms.

8.11.2 Dose Intensity

8.11.2.a Actual dose-intensity

Dose-intensity (DI) was calculated as the total dose in mg/m^2 given over all cycles, divided by the number of weeks between the first and last treatment plus a standard time of 28 days. The projected dose-intensities for the treatment arms as planned were as follows:

CEF 5-FU 250 mg/m^2/week
Epirubicin 30 mg/m^2/week
Cyclophosphamide 262.5 mg/m^2/week

CMF 5-FU 300 mg/m^2/week
Methotrexate 20 mg/m^2/week
Cyclophosphamide 350 mg/m^2/week

The actual dose intensities delivered are summarized below:

Table 10. Actual dose-intensity in mg/m^2/wk (Modified from sponsor's table 5.1, volume 2.19, page 104)

Drug received	CEF		CMF	
	No. pts.	Median	No. pts.	Median
No radiotherapy during treatment				
5-FU	352	198.58	356	282.35
Epi/MTX	352	23.80	356	19.00
CTX	352	218.75	356	352.32
Radiotherapy during treatment				
5-FU	2	151.16	4	287.86
Epi/MTX	2	18.12	4	19.70
CTX	2	177.74	4	315.50

8.11.2.b Relative dose-intensity

Relative dose intensity was defined as the ratio of the actual dose intensity to the projected DI. The following table summarizes these results:

Table 11. Relative DI (as-treated patients) (Sponsor's table 6, volume 2.19, page 61)

Drug	CEF Median [Range]	CMF Median [Range]
No radiotherapy during treatment		
	N= 352	N=356
5-FU	0.80	0.96
Epi/MTX	0.80	0.96
Cyclophosphamide	0.83	0.96
Radiotherapy during treatment		
	N=2	N=4
5-FU	0.60	0.97
Epi/MTX	0.60	0.97
Cyclophosphamide	0.66	0.96

The sponsor states that patients who received radiotherapy during treatment had a lower dose-intensity in the CEF arm than in the CMF arm. Among patients who did not receive radiotherapy with chemotherapy, a lower relative DI of epirubicin was delivered on the CEF arm compared to the DI of methotrexate on the CMF arm.

Reviewer Comments:

1. The dose-intensity of 5-FU and cyclophosphamide was greater on the CMF arm than on the CEF arm.

2. A database query demonstrated that 12 patients on CEF and 14 patients on CMF received a dose of chemotherapy after the start of radiation therapy. One patient required a dose reduction for hematologic toxicity while receiving radiation therapy. Seventeen others had dose reductions for low neutrophil counts, but the dose reductions occurred prior to the start of radiation.

3. Analyses regarding the interaction of radiation and epirubicin therapy should be considered exploratory only. Only 6 patients according to the sponsor (less than 1%) and 26 according to the reviewer's database queries violated the protocol and received combined rather than sequential chemotherapy and radiation. The DI of 5-FU and methotrexate was similar on CMF with or without radiation therapy; the DI of cyclophosphamide was decreased. On CEF, the DI of all 3 drugs was diminished in the patients who received concurrent radiation. The reasons for the dose reductions have not been documented: patients may have had prophylactic dose-reductions to avoid potential interactions between radiation and 5-FU, methotrexate, or epirubicin, or doses may have been reduced because of observed toxicity.

8.11.3 Maximum cumulative dose of epirubicin or methotrexate

The predicted maximum cumulative dose of epirubicin was 720 mg/m^2; the actual maximum cumulative dose delivered was 599.7 mg/m^2, or 83% of predicted dose. For methotrexate, these doses were 480 and 463.4 mg/m^2 (97% of predicted dose) respectively.

The following table summarizes cumulative dose delivery of these agents:

Table 12. Maximum cumulative epirubicin/methotrexate (Sponsor's table 5.3, volume 2.19, page 106)

Maximum cumulative dose (mg/m^2)	CEF N=354	CMF N=360
≤ 100	1 (0%)	1 (0%)
>100-200	3 (1%)	0
>200-300	2 (1%)	9 (3%)
>300-400	4 (1%)	25 (7%)
>400-500	34 (10%)	321 (89%)
>500-600	144 (41%)	4 (1%)
>600-700	79 (22%)	0
>700-800	87 (25%)	0

Reviewer Comments:

1. Most patients on CMF received the projected dose of methotrexate.

2. Only 25% of patients received the maximum projected dose of epirubicin (720 mg/m^2). However, 63% of the patients received between 500 and 700 mg/m^2 cumulative dose (approximately 100 mg/m^2/cycle) and 88% received greater than 500 mg/m^2, supporting the sponsor's proposed indication for "high-dose" epirubicin (100-120 mg/m^2). The median DI, which may be more informative, showed a median DI for epirubicin of 0.8, which corresponds to a median dose of 96 mg/m^2/cycle.